(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 785 212 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
23.07.1997 Bulletin 1997/30

(21) Application number: 96400146.5

(22) Date of filing: 22.01.1996

(51) Int. Cl.[6]: **C07J 7/00**, A61K 31/57, C07J 53/00, C07J 41/00 // C07J71/00, C07J21/00

(84) Designated Contracting States:
FR

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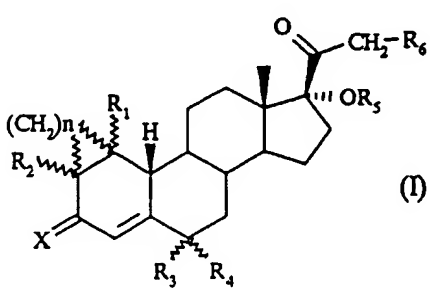
(54) **New 19-nor-pregnene derivatives**

(57) The invention relates to compounds of the formula :



(I)

wherein :

R_1, R_2, R_3, R_4 and R_6 each independently represent hydrogen or a $(C_1$-$C_6)$alkyl,
R_5 is hydrogen, a $(C_1$-$C_6)$alkyl or a group $-COR_7$ where R_7 is a $(C_1$-$C_6)$alkyl,
n is zero or one, and
X is oxygen or an hydroxyimino group,
provided that when n = 0, at least two of R_1, R_2, R_3 and R_4 are different from hydrogen and that when n = 1, R_3 and R_4 are not simultaneously hydrogen,
and to pharmaceutical compositions containing them.

These compounds are excellent progestogens and are devoid of residual androgenic activity.

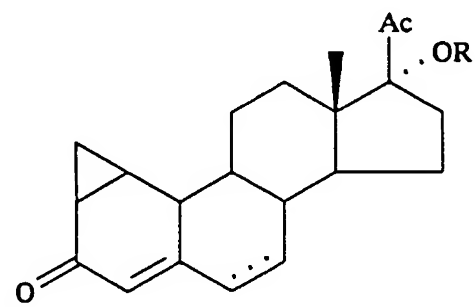
EP 0 785 212 A1

Description

The invention relates to substituted 19-nor-pregnene derivatives, methods of making these compounds and pharmaceutical compositions containing them.

The compounds according to this invention have specific and powerful progestative properties, and are devoid of residual androgenic activity.

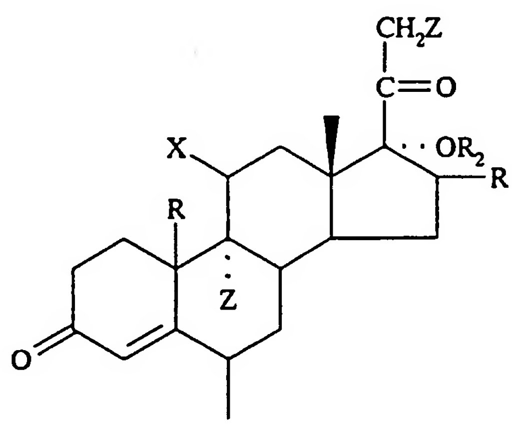
19-nor-pregnene derivatives substituted in position 1,2 - have been described in the literature. For example, FR-A-1 525 916 relates to a method of preparing compounds of the formula :



in which R is hydrogen or an acyl residue such as acetyl or hexanoyl.

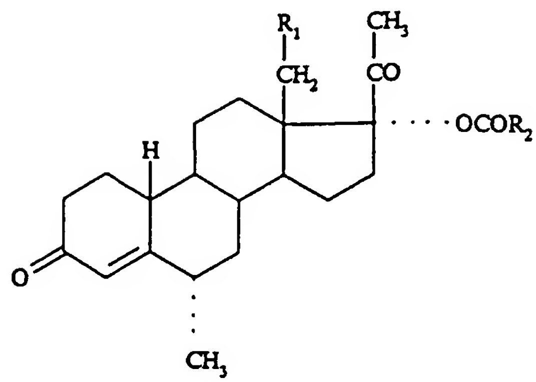
In addition, 19-nor-pregnene derivatives substituted in position 6- are described in the following documents :

* FR-A-1 524 013 which relates to 3-enol ether pregnane derivatives obtained from the 4-pregnene-3,20-diones of the formula :



among which 6α-methyl-17α-hydroxy-4-pregnene-3,20-dione may be cited ;

* DE-A-2 148 261 which describes a method of preparing 6α-methyl-19-nor-pregnenes of the formula :



in which R_1 is hydrogen or methyl and R_2 is (C_1-C_9)alkyl ; or

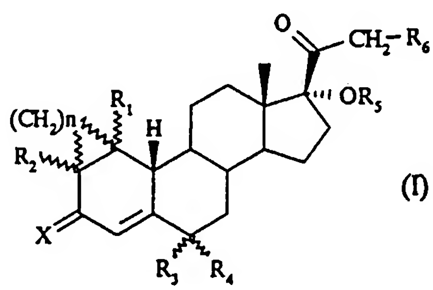
- BE 757 285 which relates to pharmaceuticals containing 3,20-dioxo-6α-methyl-17α -acetoxy-19-nor-Δ^4-pregnene.

19-nor-pregnene derivatives such as those described above usually exhibit however androgenic side effects.

On the other hand, the conversion of 17α, 20-isopropylidenedioxy-4,5-seco-3-pregnyn-5-one to 6,6-dimethyl-17α-hydroxyprogesterone is disclosed in US 3,891,677.

The Applicant has now found that 19-nor-pregnene derivatives which possess at least two substituents in position 1-, 2-, 1,2- and/or 6-, display a potent progestative activity while being devoid of residual androgenic activity.

A first aspect of this invention thus encompasses compounds having the structure represented by the following general formula (I) :



(I)

wherein :

R_1, R_2, R_3, R_4 and R_6 each independently represent hydrogen or a (C_1-C_6)alkyl,
R_5 is hydrogen, a (C_1-C_6)alkyl or a group $-COR_7$ where R_7 is a (C_1-C_6)alkyl,
n is zero or one, and
X is oxygen or an hydroxyimino group,
provided that when n = 0, at least two of R_1, R_2, R_3 and R_4 are different from hydrogen and that when n = 1, R_3 and R_4 are not simultaneously hydrogen.

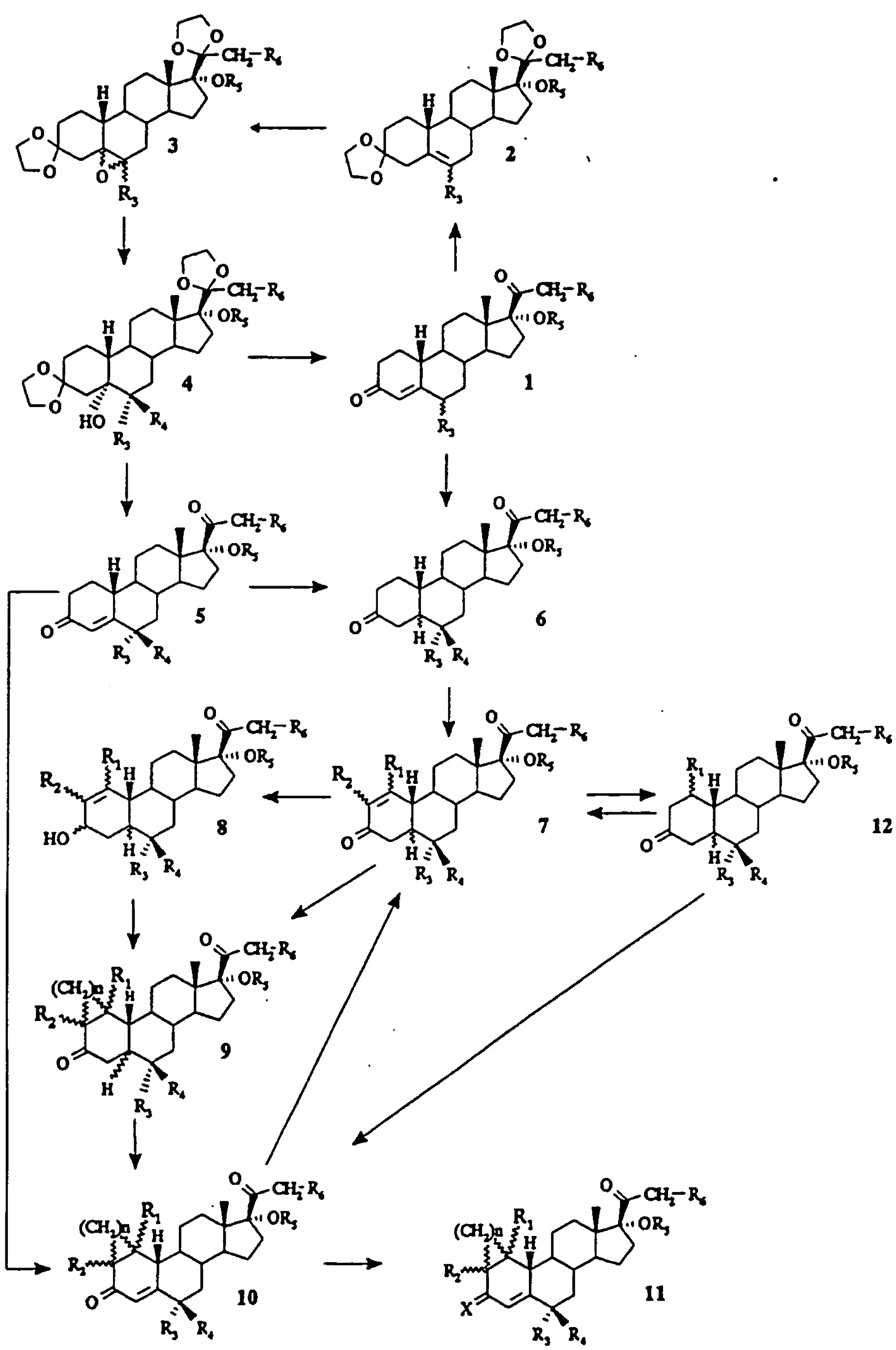
As used herein, the term "alkyl" means a branched or unbranched saturated hydrocarbon radical, such as for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl and hexyl.

As used herein the group $-COR_7$ wherein R_7 is a (C_1-C_6)alkyl includes, for example, acetyl, propionyl, butyryl, iso-butyryl, t-butyryl, valeryl and hexanoyl, acetyl being preferred.

Preferred compounds of formula (I) are those wherein R_1, R_2 and R_6 are hydrogen, R_3 and R_4 are a (C_1-C_6)alkyl, R_5 is a group $-COR_7$ and n is zero, those where X is oxygen being especially preferred. Also preferred are the compounds of formula (I) wherein R_1, R_2, R_4 and R_6 are hydrogen, R_3 is a (C_1-C_6)alkyl, R_5 is a group $-COR_7$ and n is one. Further preferred are the compounds of formula (I) wherein R_4 and R_6 are hydrogen, R_3 is a (C_1-C_6)alkyl, R_5 is a group $-COR_7$ and n is zero. Among the latter, those where R_1 is hydrogen and R_2 is a (C_1-C_6)alkyl and those where R_1 is a (C_1-C_6)alkyl and R_2 is hydrogen are also preferred, those where X is oxygen being especially preferred.

According to another aspect, the invention relates to a method of preparing the compounds of formula (I) : they can be made following the reaction scheme below in which R_1, R_2, R_3, R_4, R_5, R_6, n and X have the same meaning as set forth above.

REACTION SCHEME



Compounds **5** where R_3 and R_4 are a $(C_1\text{-}C_6)$alkyl can be prepared as follows :

Compounds **1** are prepared using a process similar to that described in DE-A-2 148 261. In the case where R_5 = -COR_7, they are saponified by sodium hydroxide in a mixture of ethanol and tetrahydrofuran. Products **1** (R_5 = H) are separated by precipitation on water followed by crystallization in an alcohol, preferably methanol or ethanol. Then, they are dissolved in toluene to which is added 1 to 10 molar equivalents of ethylene glycol, preferably 5 molar equivalents, triethylorthoformate and a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture is stirred at a temperature of about 20°C to 80°C, preferably 40°C for about 2 to 8 hours. The reaction mixture is cooled and poured into iced water and extracted with a suitable organic solvent. The residue obtained after evaporation of the solvent can be purified by crystallization or by flash-chromatography to yield the compounds **2**.

Treatment of compounds **2** with 3-chloroperoxybenzoïc acid (MCPBA) in methylene chloride gives a mixture of 5,6-oxiranes **3** which are separated by crystallization or by flash-chromatography. Addition of an excess of R_4-magnesium-halide to the compounds **3** in tetrahydrofuran at a temperature of about 20°C to 60°C for about 8 hours, and treatment of the reaction mixture with a solution of ammonium chloride and extraction with toluene and evaporation of the solvent gives the compounds **4**.

Deprotection followed by deshydratation of the tertiary hydroxy group gives the compounds **5** which can be optionally esterified by known processes used for esterification in steroid chemistry or etherified by an alkyl halide according to conventional methods of Williamson ether synthesis such as that described by B.G. Zupancic and M. Sopcic, *Synthesis*, 1979, 123 or by D.R. Benedict et al., *Synthesis*, 1979, 428-9.

Compounds **6** where R_3 is (C_1-C_6)alkyl and R_4 is hydrogen can be prepared as follows :

Compounds **6** with the 5β-H configuration are obtained by hydrogenation of compounds **1** or **5** in tetrahydrofuran, acetic acid or an alcohol such as methanol, ethanol or propanol, with palladium or a palladium or platinium derivative.

Compounds **6** with the 5α-H configuration can be obtained by chemical reduction of compounds **1** or **5** with sodium dithionite using a procedure described by F. Camps et al., *Tetrahedron Lett.*, 1986, 42, n°16, 4603-4609 or R.S. Dhillon et al., *Tetrahedron Lett.*, 1995, 36, n°7, 1107-8.

The compounds of formula (I) can be obtained as follows :

Bromination followed by dehydrobromination of the compounds **6** according to wellknown techniques (Y.J. Abul-Hajj, *J. Org. Chem.*, 1986, 51, 3059-61; C. Djerassi and C.R. Scholz, *J. Am. Chem. Soc.*, 1948, 417 ; R. Joly et al., *Bull. Soc. Chim. Fr.*, 1957, 366) gives the compounds **7** (R_1 = R_2 = H).

Compounds **5** (R_5 = H) can be transformed to their 20,20-ethanedioxy derivatives then converted to their 2-hydroxymethylene sodium salt and alkylated using an alkyl iodide such as methyl iodide, ethyl iodide or propyl iodide following the method described by N.W. *Atwater* et al. in *J. Org. Chem.*, 1961, 23, 3077-83 to obtain compounds **10** (R_1 = H, R_2= alkyl, n=0).

Optionally, chemical reduction by hydrogenation of the 4,5-double bond of compounds **10** (R_1 = H, R_2 = alkyl, n = 0), followed by bromination/dehydrobromination gives compounds **7** (R_1 = H, R_2 = alkyl).

Addition of a lithium dialkylcuprate $LiCu(R_1)_2$ or of the corresponding alkylmagnesium halide under copper catalysis (for example CuI, CuCl or CuCN) to compounds **7** (R_1 = R_2 = H) gives compounds **12** (R_1 = alkyl) which can be converted to compounds **10** (R_1 = alkyl, R_2 = H, n = 0) using well-known techniques for the introduction of 4,5-double bond in steroid chemistry, or transformed to compounds **7** (R_1 = alkyl, R_2 = H) by dehydrogenation or by bromination/dehydrobromination. Compounds **12** can also be alkylated in position 2- by a similar process to obtain compounds **10** (R_2 = alkyl, n = 0) which are then converted to compounds **7** (R_1 = R_2 = alkyl) as described above.

Compounds **9** (R_1 = H or alkyl, R_2 = H or alkyl, n = 1) are prepared by reaction of compounds **7** (R_1 = H or alkyl, R_2 = H or alkyl) with a dimethylsulfoxonium methylide produced by the reaction of trimethylsulfoxonium iodide (with a base preferably) with sodium hydride in tetrahydrofuran, dimethylformamide or dimethylsulfoxide. They can also be prepared by reaction of compounds **7** with diazomethane catalyzed by palladium or copper derivatives. Alternatively, compounds **7** (R_1 = H or alkyl, R_2 = H or alkyl) can be reduced with sodium borohydride in the presence of cerium chloride into compounds **8** (R_1 = H or alkyl, R_2 = H or alkyl) which are submitted to a Simmons-Smith reaction according to various known described procedures (H.E. Simmons and R.D. Smith, *J. Am. Chem. Soc.*, 1958, 80, 5323 ; H.E. Simmons and R.D. Smith, *J. Am. Chem. Soc.*, 1959, 81, 4256 ; Org. Synthesis, 1961, 41, 72 ; J. Furukawa et al., *Tetrahedran Lett.*, 1966, 3353 ; J. Furukawa et al., *Tetrahedron* 1968, 24, 53 ; S.E. Denmark and Edwards, *J. Org. Chem.*, 1991, 56, 6974-81).

Oxidation of the 3-hydroxy group of compounds **8** with various oxidizing agents such as CrO_3/pyridine gives compounds **9**.

Compounds **9** (R_1 = H or alkyl, R_2 = H or alkyl, n = 0 or 1) are converted to their silyl enol ether and dehydrogenated with palladium acetate in refluxing acetonitrile to give compounds **10**. Alternatively, the 4,5-double bond can be introduced by bromination followed by dehydrobromination using a process similar to that described above for compounds **7**. Condensation of compounds **10** with hydroxylamine hydrochloride in a mixture of dioxane and pyridine gives compounds **11**.

The compounds according to this invention have specific and powerful progestative properties. Therefore they are useful for the treatment of a variety of endocrine-gynaecological disorders, either related to an oestrogen/progesterone imbalance, including menstrual disorders (spaniomenorrhea, oligomenorrhea, secondary amenorrhea, premenstrual

tension, headache, water retention, mood alteration), breast disorders (cyclical mastalgia, benign breast disease, breast tumors), endometrial diseases (hyperplasia, pre-malignant alteration tumors) ; or conditions requiring inhibition of gonadotropic/gonadal secretions: endometriosis, polycystic ovary syndrome in women, prostate diseases in men.

On the other hand, the compounds according to the invention can be used as contraceptive agents, either alone or in combination with an affective amount of sex steroid such as oestradiol, ethinyl oestradiol or testosterone, and again alone or in combination with an oestrogen for hormonal replacement therapy in postmenopausal women.

The progestative activity of the compounds according to the present invention can be assessed mainly in two specific experimental models the affinity for the progesterone receptor (PR) *in vitro*, and the endometrial tranformation of the rabbit uterus *in vivo*.

Human PR are readily available in high amounts from the T47-D cell line in culture (M.B. Mockus et al., *Endocrinology*, 1982, 110, 1564-1571). Relative binding affinities (RBA) for the human T47-D cell PR are determined as previously described (J. Botella, et al., *J. Steroid Biochem. Molec. Biol.*, 1994, 50, 41-47) using [^{3}H]-ORG 2058 as a labelled specific ligand (G. Fleischmann and M. Beato, *Biochim. Biophys. Acta*, 1978, 540, 500-517) and nomegestrol acetate as a non-radioactive reference progestin.

Competitive incubations were performed against 2 nM of [^{3}H]-ORG 2058 for 3 hours at 4°C with six different concentrations of non-labelled steroid, chosen between 4 and 256 nM following a $1/2^n$ dilution scheme. Displacement curves were fitted for each experiment, and the concentration inhibiting 50% of the specific binding of [^{3}H]-ORG 2058 was calculated for each curve (IC_{50}).

Table 1

Relative binding affinity to human T47-D cell progesterone receptor			
Progestin	IC_{50}[(a)] in nM	(n)	RBA
Nomegestrol acetate	8.9 ± 2.0	(8)	100 %
Compound of example 1	27.8 ± 2.0	(4)	32 %
Compound of example 4	22.8 ± 1.7	(4)	39 %
Compound of example 5	17.7 ± 2.4	(4)	50 %

(a) mean ± s.e.m. ;
(n) number of experiments

One specific pharmacological test has been standardized *in vivo* for the detection and quantitation of pseudogestagenic activity since the mid-30's : it is based on the property of the uterus of estrogen-primed immature female rabbits to respond to very slight amounts of progestin by a typical endometrial transformation into a densely packed and interlaced epithelial network called "dentelle". The original test schedule, which includes 6 days of estrogen priming (total subcutaneous dose of 30 μg/rabbit of oestradiol benzoate) followed by 5 days of progestative treatment, was designed as early as 1930 by C. Clauberg, *Zentr. Gynäkol.* 1930, 54, 2757-2770. The semi-quantitative scale used to grade the intensity of the microscopical appearance of the dentelle was set up by M.K. McPhail, *J. Physiol* (London), 1934, 83, 145-156. This overall Clauberg-McPhail procedure has been extensively used to screen steroids for putative progestative activity *in vivo* and is still part of the basic hormonal profile of any new progestin such as norgestimate (A Phillips et al., *Contraception*, 1987, 36, 181-192), or desogestrel (J. Van der Vies and J. De Visser, *Arzneim. Forsch./Drug Res.*, 1983, 33, 231-236).

The progestative potency is inversely related to the dose needed to induce a half-maximal stimulation of the dentelle, i.e. to record a mean McPhail grade equal to 2. This ED_{50} is deduced from the dose-response curve and expressed in total dose/rabbit/5 days. All compounds were tested only following oral administration by gavage, in suspension in a carboxy-methylcellulose solution. The maximal dose administered was 1 mg, roughly corresponding to 5 times the ED_{50} of nomegestrol acetate, a potent orally active 19-norprogesterone-derived progestin (J. Paris et al., *Arzneim. Forsch./Drug Res.*, 1983, 33, 710-715).

Table 2

Clauberg-McPhail test by oral administration (gavage)			
Progestin	ED_{50}[(a)] (mg/rabbit/5 days)	(n)	Relative activity
Nomegestrol acetate	170 ± 41	(5)	100 %
Example 1	152 ± 28	(3)	112 %
Example 4	66 ± 11	(2)	258 %
Example 5	> 750 ± 6.0	(1)	< 17 %

(a) mean ± s.e.m. ;
(n) number of experiments

The residual androgenic potential is an important feature to be evaluated for any new progestin, because it is highly predictive of androgenie side-effects in women. One pharmacological model of androgenic activity has been standardized to screen steroids or related compounds in immature castrated male rats, using the hypertrophy of the ventral prostate and of the seminal vesicle as the endpoint, following 10 daily administrations (R.I. Dorfman, in *Methods in Hormone Research*, volume 2, London, Academic Press, 1962 : 275-313 ; A.G. Hilgar and D.J. Hummel, *Andragenic and Myogenic Endocrine Bioassay Data*, U.S. Department of Health, Education and Welfare, Washington D.C., 1964). Medroxyprogesterone acetate is a 6α-methylpregnene derivative which, besides its main progestative activity, is well-known for its weak androgenic properties (M. Tausk and J. de Visser, In *International Encyclopedia of Pharmacology and Therapeutics*, Section 48 : Progesterone, Progestational Drugs and Antifertility Agents, volume II, OXFORD, Pergamon Press, 1972 : 35-216); it was therefore chosen as a reference compound in the testing for residual androgenic activity of some compounds according to the invention .

Compounds of examples 1 and 4 were tested for residual androgenic activity in the immature castrated male rat model by gavage (PO), in comparison, respectively, with medroxyprogesterone acetate and cyproterone acetate (a 1,2 α-cyclomethylene pregnene derivative with potent progestative activity) ; testosterone was used as a standard androgenic agent by subcutaneous injection (SC).

Table 3

Residual androgenic activity of the compound of example 1			
Steroid	Dose (mg/animal/day)	Ventral Prostate (mg)	Seminal Vesicle (mg)
Castrated controls	-	12.0 ± 0.9	12.3 ± 0.7
Testosterone, SC	0.05	90.4 ± 4.4***	90.3 ± 6.7***
Medroxyprogesterone acetate, PO	20	29.1 ± 1.4***	19.9 ± 1.8**
Example 1, PO	20	13.0 ± 0.3 ns	10.4 ± 0.5 ns
mean ± s.e.m. of 8 animals per group ;			

** p < 0.001 and
*** p < 0.001
ns : not statistically different from controls.

Table 4

Residual androgenic activity of the compound of example 4			
Steroid	Dose (mg/animal/day)	Ventral Prostate (mg)	Seminal Vesicle (mg)
Castrated controls	-	11.8 ± 0.6	10.4 ± 0.6
Testosterone, SC	0.05	80.9 ± 3.4***	79.0 ± 5.3***
Cyprotérone acetate, PO	20	15.3 ± 1.3*	11.3 ± 0.6 ns
Example 4, PO	20	12.1 ± 0.4 ns	11.2 ± 0.5 ns
mean ± s.e.m. of 7 or 8 animals per group ;			

* $p < 0.05$ and
*** $p < 0.001$
ns : not statistically different from controls.

The compounds of examples 1 and 4 were totally inactive on the growth of male accessory sex organs (Tables 3 and 4). The stimulatory effect of cyproterone acetate was very weak and limited to the ventral prostate, at the border of statistical significance (Table 4), while medroxyprogesterone acetate caused both organs to more or less double in weight (Table 3).

Thus, the compounds according to the present invention are potent progestogens devoid of any residual androgenic activity.

Thus according to another aspect, the invention relates to pharmaceutical compositions containing an effective amount of a compound of formula (I), mixed with suitable pharmaceutically acceptable excipients. Said compositions may further comprise an effective amount of an oestrogen.

Another aspect of the invention comprises a method of treating or preventing endocrine - gynaecological disorders, and a method of inhibiting gonadotropic/gonadal secretions.

The compounds according to the present invention can be administered at therapeutically effective dosage for each condition mentioned above. Administration of the active compounds described herein can be via any of the accepted modes of administration for agents that serve similar utilities.

The usual, necessary daily dose of the compound according to the invention will be in the range of 0.001 to 1 mg/kg of body weight per day of the active compound of formula (I). Most conditions respond to a treatment comprising a dosage level on the order of 0.002 to 0.2 mg/kg of body weight per day. Thus, for administration to a 50 kg person, the dosage range would be about 1 mg per day, preferably between about 0.1 to 10 mg per day.

Depending on the specific clinical status of the disease, administration can be given via any accepted systemic delivery system, for example, via oral route or parenteral route such as intravenous, intramuscular, subcutaneous or percutaneous route, or vaginal, ocular or nasal route, in the form of solid, semi-solid or liquid dosage forms, such as for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, cream, gel, implant, patch, pessary, aerosols, collyrium, emulsions or the like, preferably in unit dosage forms suitable for easy administration of fixed dosages. The pharmaceutical compositions will include a conventional carrier or vehicle and a compound of formula (I) and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

The compounds of this invention are generally administered as a pharmaceutical composition which comprises a pharmaceutical vehicle in combination with a compound of Formula (I). The level of the drug in a formulation can vary within the full range employed by those skilled in the art, e.g., from about 0.01 weight percent (wt%) to about 99.99 wt% of the drug based on the total formulation and about 0.01 wt% to 99.99 wt% excipient.

The preferred mode of administration, for the conditions mentioned above, is oral administration using a convenient daily dosage regimen which can be adjusted according to the degree of the complaint. For said oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of the selected compound of formula (I) in any of the currently used excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain between 0.01 wt% and 99.99 wt% of the active compound

according to this invention.

Preferably the compositions will have the form of a sugar coated pill or tablet and thus they will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like ; a disintegrant such as starch or derivatives thereof ; a lubricant such as a magnesium stearate and the like ; and a binder such as a starch, polyvinylpyrrolidone, acacia gum, gelatin, cellulose and derivatives thereof, and the like.

The invention is now illustrated by the examples below. In these examples, the following abbreviations are used :

s : singlet
d : doublet
t : triplet
q : quadruplet
m : multiplet
dd : doubled doublet
bs : broad singlet

EXAMPLE 1 : 17α-acetoxy-6,6-dimethyl-3,20-dioxo-19-nor-pregna-4-ene (5)

A/ 17α-hydroxy-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene (1)

To a solution of 17α-acetoxy-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene (100 g, 268 mmol.) in absolute ethanol and tetrahydrofuran (200 mL) was added, in 45 min. at room temperature, 1N sodium hydroxyde (300 mL, 300 mmol.). The solution was stirred (8 hours) and poured into iced water (4000 mL). The precipitate was filtered and dried at 50°C over vacum (yield: 70 g, 78.9 %), mp : 172°C.

^{1}H-NMR ($CDCl_3$,δ) : 0.79 (s, 3H) ; 1.25 (d, 3H) ; 2.29 (s, 3H) ; 2.68 (m, 1H) ; 5.87 (s, 1H).

B/ Bis-[3,3-20,20-ethanedioxy]-17α-hydroxy-6-methyl-19-nor-pregna-5-ene (2)

To a suspension of compound 1 (70 g, 211 mmol.) in anhydrous ethylene glycol (1000 mL), acetonitrile (700 mL) and triethylorthoformate (105 mL, 633 mmol.) was added para-toluenesulfonic acid monohydrate (5.25 g, 27.6 mmol.). The mixture was stirred (2 hours) and neutralizated by triethylamine (8 mL, 57.4 mmol.). After concentration to 1000 mL, the suspension was poured into water (4000 mL). The precipitate was filtered and dried at 60°C over vacum (yield : 81 g, 92.1 %), mp : 214°C.

^{1}H-NMR ($CDCl_3$,δ) : 0.85 (s, 3H) ; 1.40 (s, 3H) ; 1.65 (s, 3H) ; 2.80 (m, 1H) ; 4.00 (m, 8H).

C/ 5α,6α-epoxy-bis[3,3-20,20-ethanedioxy]-17α-hydroxy-6β-methyl-19-nor-pregnane (3)

To a solution of compound **2** (70 g, 167 mmol.) in methylene chloride (800 mL) was added a 80 % solution of 3-chloroperoxybenzoïc acid (43.29 g, 200.17 mmol.) in methylene chloride (250 mL). The reaction mixture was stirred for 1 hour. The precipitate was filtered and the organic phase was washed with $NaHSO_3$ and with a solution of hydrogen sodium carbonate. The organic phase was dried (Na_2SO_4), concentrated and the residue was flash-chromatographed on silica gel using toluene/ethyl acetate as eluting solvent to give 20.3 g of the title compound (yield : 27.63 %), mp : 220°C.

^{1}H-NMR ($CDCl_3$,δ) : 0.80 (s, 3H) ; 1.25 (s, 3H) ; 1.35 (s, 3H) ; 4.00 (m, 8H).

D/ Bis[3,3-20,20-ethanedioxy]-5α,17α-dihydroxy-6,6-dimethyl-19-nor-pregnane (4)

To a solution of compound 3 (30 g, 69 mmol.) in tetrahydrofuran (1200 mL) was added 1.4 M methyl magnesium bromide in a tetrahydrofuran/toluene mixture (250 mL, 345 mmol.). The solution was stirred at reflux overnight. The mixture was poured into a solution of ice and saturated ammonium chloride (1000 mL). The reaction mixture was extracted with toluene, washed by water and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was chromatographed using toluene/ethyl acetate as eluting solvent (yield: 15.4 g, 49.55 %), mp : 212°C.

^{1}H-NMR ($CDCl_3$,δ) : 0.85 (s, 3H) ; 0.95 (s, 6H) ; 1.35 (s, 3H) ; 4.00 (m, 8H).

E/ 17α-acetoxy-6,6-dimethyl-3,20-dioxo-19-nor-pregna-4-ene

To the above compound (30.8 g, 68.33 mmol.) in acetone (300 mL) and water (30 mL) was added para-toluenesulfonic acid monohydrate (1.33 g, 7 mmol.). The reaction mixture was stirred at room temperature for 5 hours. After neutralisation with $NaHCO_3$, the mixture was poured into iced water (100 mL) and extracted twice with methylene chloride. The organic layer was washed with water, dried (Na_2SO_4) and concentrated to give 24.3 g of 5α,17α-dihydroxy-6,6-dimethyl- 3,20-dioxo-19-nor-pregnane (yield : 98.2 %), mp : 224°C.

^{1}H-NMR ($CDCl_3$,δ) : 0.75 (s, 3H) ; 0.91 (s, 3H) ; 1.08 (s, 3H) ; 2.29 (s, 3H).

To a solution of this compound (15 g, 41.20 mmol.) in acetic acid (120 mL) was added a few drops of H_2SO_4 (98 %). The mixture was heated at 60°C for 5 hours. Then, it was poured into a solution saturated with $NaHCO_3$ and extracted with methylene chloride. The organic phase was dried (Na_2SO_4) and evaporated to give 12.3 g of 17α-hydroxy-6,6-dimethyl-3,20-dioxo-19-nor-pregna-4-ene (yield 96.3 %), mp : 172°C.

^{1}H-NMR ($CDCl_3$,δ) : 0.79 (s, 3H) ; 1.15 (s, 6H) ; 2.09 (s, 3H) ; 5.97 (s, 1H).

To a solution of this compound (12.3 g, 35.7 mmol.) in acetic acid (120 mL) and acetic anhydride (70 mL) was added para-toluenesulfonic acid (2.5 g, 13.2 mmol.). The mixture was stirred for 12 hours at room temperature. After completion of the reaction, the excess of anhydride was decomposed by water. The mixture was extracted with methylene chloride and washed with a 1N aqueous NaOH solution. The organic phase was dried (Na_2SO_4) and concentrated. The residue was flash-chromatographed using toluene/ethyl acetate as eluting solvent and recrystallized in diisopropyloxide (yield : 7 g, 50.81 %), mp : 200°C.

^{1}H-NMR ($CDCl_3$,δ) : 0.71 (s, 3H) ; 1.18 (s, 6H3) ; 2.05 (s, 3H) ; 2.11 (s, 3H) ; 5.99 (s, 1H).

EXAMPLES 2 AND 3 : 17α-acetoxy-6β-ethyl-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene (**5.a**) and 17α-acetoxy-6β-propyl-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene (**5.b**)

Starting from compound **3** using the process described for compound **5** but replacing the methyl magnesium bromide by ethyl or propyl magnesium bromide the following compounds were obtained : 17α-acetoxy-6β-ethyl-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene, mp : 160°C (example 2).

^{1}H-NMR ($CDCl_3$,δ) : 0.7 (s, 3H) ; 0.72 (t, 3H) ; 1.08 (s, 3H) ; 2.05 (s, 3H) ; 2.11 (s, 3H) ; 5.95 (s, 1H); and 17α-acetoxy-6β-propyl-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene (example 3).

EXAMPLE 4 : 17α-acetoxy-1α,2α-methylene-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene (**10**)

A_1/ 17α-acetoxy-6α-methyl-3,20-dioxo-19-nor-pregnane (**6**)

To a solution of 17α-acetoxy-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene (10 g, 26.84 mmol.) in dioxane (100 mL) and water (100 mL) containing $NaHCO_3$ (14.65 g, 174.46 mmol.) was added sodium dithionite (7.9 g, 38.5 mmol.) and the reaction mixture was stirred at 50°C for 1 hour, during which time additional sodium dithionite was added in three portions of 7.9 g each. The reaction mixture was cooled to room temperature and cold water was added until the solution became clear. Thereafter, the solution was extracted with diethyloxide, dried (Na_2SO_4), concentrated in vacuo and flash-chromatographed (toluene/ethyl acetate) to give 2 g of compound **6** (yield : 20 %), mp : 202°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.65 (s, 3H) ; 0.86 (d, 3H) ; 2,03 (s, 3H) ; 2.09 (s, 3H) ; 2.31 (m, 3H) ; 2.62 (m, 1H) ; 2.90 (m, 1H).

B_1/ 17α-acetoxy-6α-methyl-3,20-dioxo-19-nor-pregna-1-ene (**7**)

A mixture of compound **6** (20 g, 53.40 mmol.) and $Pd(OAc)_2$ (14.38 g, 64.05 mmol.) in acetonitrile (300 mL) was refluxed for 8 hours. After cooling, the palladium was filtered and the solvent evaporated. The residue was flash-chromatographed on silica gel using toluene/ethyl acetate (8/2) as eluting solvent to give 7 g of compound **7** (yield : 35 %), mp : 186-188°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.69 (s, 3H) ; 0.93 (d, 3H) ; 2.07 (s, 3H) ; 2.12 (s, 3H) ; 2.76 (d, 1H) ; 2.94 (m, 1H) ; 6.02 (dd, 1H) ; 7.11 (dd, 1H).

C_1/ 17α-acetoxy-1α,2α-methylene-6α-methyl-3,20-dioxo-19-nor-pregnane **(9)**

To a stirred suspension of trimethylsulfoxonium iodide (7.68 g, 34.91 mmol.) in dimethyl sulfoxide (50 mL) was added sodium hydride in oil (60 %) (1.53 g, 38.2 mmol.). The mixture was stirred at 25°C for 1 hour, and then compound **7** (2.97 g, 7.98 mmol.) was added. After 3 hours, the reaction mixture was poured in water. Collection of the resulting solid by filtration and flash-chromatography on silica gel using toluene/ethyl acetate as eluting solvent gave 1 g of compound **9** (yield : 33 %), mp : 204°C.

^{1}H-NMR ($CDCl_3$, δ): 0.68 (s, 3H) ; 0.84 (d, 3H) ; 2.02 (s, 3H) ; 2.12 (s, 3H) ; 2.52 (dd, 1H) ; 2.92 (m, 1H).

D_1/ 17α-acetoxy-1α,2α-methylene-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene

To a solution of compound **9** (4 g, 10.35 mmol.) in tetrahydrofuran (80 mL) was added portionwise pyridinium tribromide (3.83 g, 11.38 mmol.). After 30 min. the mixture was filtered, evaporated and the residue extracted with methylene chloride, washed with water and dried (Na_2SO_4). Evaporation of the solvent gave 5 g of a brown oil to which dimethyl formamide (80 mL), Li_2CO_3 (1.53 g, 20.70 mmol.) and LiBr (0.90 g, 10.35 mmol.) were added. The mixture was heated at 140°C for 1 hour. After cooling the salts were removed by filtration and the solvent concentrated under reduced pressure. The residue was extracted with methylene chloride, washed with water and dried on Na_2SO_4. Flash-chromatography on silica gel using toluene/ethyl acetate as eluting solvent gave 2 g of the title compound (yield : 50 %), mp : 210°C.

^{1}H NMR ($CDCl_3$,δ) : 0.71 (s, 3H) ; 1.09 (d, 3H) ; 2.04 (s, 3H) ; 2.12 (s, 3H) ; 2.42 (m, 1H) ; 2.84 (m, 1H) ; 5.65 (s, 1H).

A_2/ Alternatively, compound **10** can also be prepared from 17α-acetoxy-6α-methyl-3,20-dioxo-19- nor-5β-pregnane obtained from hydrogenation of 17α-acetoxy-6α-methyl-3,20-dioxo-19- nor-pregna-4-ene in acetic acid using $Pd(OH)_2$ as catalyst.

B_2/ Then, to a cooled solution of the resulting compound (20 g, 53 mmol.) in THF (200 mL) was added 17.1 g (53 mmol.) of pyridinium tribromide. After 2 hours the mixture was filtered, poured on iced water and extracted with methylene chloride. Evaporation of the solvent gave 23.8 g (yield : 98.3 %) of crude 17α-acetoxy-2α-bromo-6α-methyl-3,20-dioxo-19-nor-5β-pregnane which was dehydrobrominated following the conditions described above in step D_1 to give 15.9 g (yield: 80 %) of 17α-acetoxy-6α-methyl-3,20-dioxo-19-nor-5β-pregna-1-ene **(7.a)**, mp: 184°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.69 (s, 3H) ; 0.9 (d, 3H) ; 2.02 (s, 3H) ; 2.1 (s, 3H) ; 2.9 (m, 1H) ; 6.02 (d, 1H).

C_2/ 17α-acetoxy-3α-hydroxy-6α-methyl-20-oxo-19-nor-5β-H-pregna-1-ene **(8.a)**

To 10 g (27 mmol.) of the compound obtained in step B_2 and 12 g of cerium chloride heptahydrate in methanol (200 mL) cooled to 0°C were added, portionwise, 2.5 g (54 mmol.) of sodium borohydride. Then, the mixture was stirred for 1 hour at room temperature, poured on iced water and the precipitate collected by filtration, dried and recrystallized from diisopropyloxide to give 3.6 g of **8.a** (yield: 35.6 %), mp : 211°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.65 (s, 3H) ; 0.92 (d, 3H) ; 2.0 (s, 3H) ; 2.1 (s, 3H) ; 2.9 (m, 1H) ; 4.32 (m, 1H) ; 5.64 (d, 1H) ; 5.96 (dd, 1H).

D_2/ 17α-acetoxy-1α,2α-methylene-6α-methyl-3,20-dioxo-19-nor-5β-pregnane **(9.a)**

To 3 g (80 mmol.) of compound **8.a** in dichloroethane (200 mL) at -25°C were added dropwise 40 mL of a 1N solution of diethylzinc in hexane followed by 6.45 mL of diiodomethane. After 1 night at room temperature, the white mixture was poured in a solution of ammonium chloride and extracted with methylene chloride. Evaporation of the solvent gave a residue which was flash-chromatographed on silica gel using toluene/ethyl acetate as eluting solvent to give 1.43 g of the 3α-hydroxy-1α,2α-methylene derivative.

^{1}H-NMR ($CDCl_3$, δ) : 0.4 (m, 2H) ; 0.68 (s, 3H) ; 0.85 (d, 3H) ; 2.05 (s, 3H) ; 2.16 (s, 3H) ; 2.9 (m, 1H) ; 4.13 (m, 1H).

Oxidation of the 3α-hydroxy-1α,2α-methylene derivative in acetone with Jones' reagent gave 1 g of **9.a** (70 % yield) which was converted to **10** by the same procedure than that described in step D_1.

EXAMPLE 5 : 17α-acetoxy-1β,2β-methylene-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene **(10.a)**

A/ 17α-acetoxy-6α-methyl-3,20-dioxo-19-nor-5β-pregnane **(6.a)**

Compound **1** (20 g, 53.69 mmol.) in methanol (200 mL) containing acetic acid (5 mL) and 20 % $Pd(OH)_2$ (200 mg) on charcoal were hydrogenated under 1 atm. H_2. Filtration of the catalyst and removal of the solvent followed by crystallization in ethyl acetate gave 12.06 g of compound **6.a** (yield: 60 %), mp : 204°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.63 (s, 3H) ; 0.80 (d, 3H) ; 2.01 (s, 3H) ; 2.10 (s, 3H) ; 2.91 (m, 1H)

B/ 17α-acetoxy-6α-methyl-3,20-dioxo-19-nor-5β-pregna-1-ene **(7.a)**

Compound **7.a** was prepared in 30 % yield following the procedure described in example 4, step B_2, mp : 184°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.68 (s, 3H) ; 0.92 (d, 3H) ; 2.03 (s, 3H) ; 2.09 (s, 3H) ; 2.92 (m, 1H) ; 6.03 (d, 1H) ; 7.16 (dd, 1H).

C/ 17α-acetoxy-1β,2β-methylene-6α-methyl-3,20-dioxo-19-nor-5β-pregnane **(9.b)**

Compound **9.b** was prepared in 30 % yield following the procedure described in example 4, steps C_1 and D_1, mp : 174-176°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.61 (s, 3H) ; 0.79 (d, 3H) ; 2.01 (s, 3H) ; 2.11 (s, 3H) ; 2.88 (m, 1H).

D/ 17α-acetoxy-1β,2β-methylene-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene

This compound was prepared in 19 % yield following the procedure described in example 4, step D_1, mp : 247°C.

IR (KBr, cm^{-1}) : 1730 νC = O ; 1720 νC = O ; 1644 νC = O ; 1458 νC = C. ^{1}H-NMR ($CDCl_3$, δ) : 0.59 (s, 3H) ; 0.94 (d, 3H) ; 1.95 (s, 3H) ; 2.00 (s, 3H) ; 2.37 (d, 1H) ; 2.82 (m, 1H) ; 5.52 (s, 1H)

EXAMPLES 6 AND 7 : 17α-acetoxy-1β,2β-methylene-3E-hydroxyimino-6α-methyl-20-oxo- 19-nor- pregna- 4-ene **(11)** and 17α-acetoxy-1β,2β-methylene-3Z-hydroxyimino-6α-methyl-20-oxo- 19-nor- pregna-4-ene **(11.a)**

To a solution of compound **10.a** (1.24 g, 3.25 mmol.) in dioxane (50 mL) were added successively hydroxylamine hydrochloride (0.45 g, 6.46 mmol.) and pyridine (3.1 mL).

The mixture was heated to reflux for 1.5 hour. Then, the reaction mixture was poured into iced water and acidified with a 1N HCl solution. Extraction with methylene chloride and evaporation of the solvent gave 1.29 g of a crude product which was flash-chromatographed using toluene/ethyl acetate as eluting solvent.

The first product eluted was the E isomer and crystallized from ethanol (0.3 g, yield : 28.8 %), mp : 172°C (example 6).

^{1}H-NMR ($CDCl_3$, δ) : 0.5 (q, 1H) ; 0.65 (s, 3H) ; 1.02-1.04 (d, 3H) ; 2.05 (s, 3H) ; 2.12 (s, 3H) ; 2.95 (m, 2H) ; 5.62 (s, 1H).

The second product eluted was the Z isomer and it was crystallised from a mixture of absolute ethanol and diisopropyl ether (0.080 g, yield : 7.7 %), mp: 168°C (example 7).

^{1}H-NMR ($CDCl_3$, δ) : 0.681 (s, 3H) ; 1.08-1.1 (d, 3H) ; 2.05 (s, 3H) ; 2.12 (s, 3H) ; 2.95 (m, 1H) ; 6.32 (s, 1H).

EXAMPLE 8 : 17α-acetoxy-2α,6α-dimethyl-3,20-dioxo-19-nor-pregna-4-ene **(10.b)**

A solution of 20,20-ethanedioxy-17α-hydroxy-6α-methyl-19-nor-pregna-4-ene (prepared from compound **5**, R_3=CH_3, R_5=H, R_6=H, R_4=H) (10 g, 26.7 mmol.), sodium methylate (8.25 g, 152.2 mmol.) and ethyl formate (12.71 g, 171.6 mmol.) was stirred at room temperature for 4 hours. Then, the precipitate was filtered, washed with diethyloxide to yield 11 g of the crude 2-hydroxymethylene sodium salt derivative which was used without further purification.

To this compound (11 g) in acetone (180 mL) were added potassium carbonate (13.5 g, 98 mmol.) and methyl iodide (46.4 g, 326.8 mmol.) and the mixture was stirred at room temperature for 12 hours. After filtration, the organic solution was poured into a solution of 1N NaOH, extracted with methylene chloride, dried (Na_2SO_4) and concentrated

in vacuo to give a crude product (12.70 g) to which was added methanol (70 mL) and a solution of 6.66 g (166.5 mmol.) of sodium hydroxyde in water (6.6 mL) and the solution was refluxed for 5 hours. After cooling, the mixture was acidified to pH = 1 with a solution of 1N HCl and then, poured into water. The precipitate was collected, washed with water and dried. Flash-chromatography on silica gel (toluene/ethyl acetate) gave 4.10 g of the 17α-hydroxy derivative of the title compound (yield : 40 %).

^{1}H-NMR ($CDCl_3$, δ) : 0.78 (s, 3H) ; 1.10 (d, 6H) ; 2.27 (s, 3H) ; 2.68 (t, 1H) ; 2.83 (s, 1H) ; 5.87 (s, 1H).

It was converted to its acetyl derivative following the procedure described for compound **6.a** in 30% yield, mp : 144°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.7 (s, 3H) ; 1.13 (d, 6H) ; 2.06 (s, 3H) ; 2.12 (s, 3H) ; 2.95 (t, 1H) ; 5.88 (bs, 1H).

EXAMPLE 9 : 17α-acetoxy-1α,6α-dimethyl-3,20-dioxo-19-nor-pregn-4-ene **(10.c)**

A/ 17α-acetoxy-1α,6α-dimethyl-3,20-dioxo-19-nor-pregnane **(12)**

To a suspension of copper chloride (1.59 g, 16.11 mmol.) in tetrahydrofuran (400 mL) at 0°C under N_2 was added slowly methyl lithium (1.6 N) in diethyloxide (28.76 mL, 32.21 mmol.). After 1 hour, a solution of compound **7** (5 g, 13.42 mmol.) in tetrahydrofuran (40 mL) was added to the mixture at 0°C. After 6 hours, a saturated solution of ammonium chloride was carefully added dropwise over 10 min. This mixture was stirred for 15 min., then extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated. The resulting crude product was flash-chromatographed (toluene/ethyl acetate) to give 3 g of **12** (yield : 57 %), mp : 183°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.66 (s, 3H) ; 0.81 (d, 3H) ; 0.86 (d, 3H) ; 2.01 (s, 3H) ; 2.10 (s, 3H) ; 2.90 (t, 1H).

B/ Using the same procedure than that described for the preparation of compound **10** from compound **9**, compound **10.c** was obtained in 35% yield, mp : 209°C

^{1}H-NMR ($CDCl_3$, δ) : 0.81 (s, 3H) ; 0.90 (d, 3H) ; 1.15 (d, 3H) ; 2.06 (s, 3H) ; 2.12 (s, 3H) ; 2.95 (t, 1H) ; 5.95 (s, 1H).

EXAMPLE 10: 17α-acetoxy-1β,6α-dimethyl-3,20-dioxo-19-nor-pregna-4-ene **(10.d)**

A/ 17α-acetoxy-1β,6α-dimethyl-3,20-dioxo-19-nor-5β-pregnane **(12.a)**

Compound **12.a** was prepared in 60 % yield following the procedure described for compound **12**, mp : 142°C.

^{1}H-NMR ($CDCl_3$, δ) : 0.66 (s, 3H) ; 0.83 (d, 3H) ; 0.98 (d, 3H) ; 2.06 (s, 3H) ; 2.14 (s, 3H) ; 2.92 (t, 1H).

B/ Using the same procedure than that described for the preparation of compound **10** from compound **9**, compound **10.d** was obtained in 40 % yield, mp: 187°C

^{1}H-NMR ($CDCl_3$, δ) : 0.69 (s, 3H) ; 1.06 (d, 3H) ; 1.09 (d, 3H) ; 2.06 (s, 3H) ; 2.12 (s, 3H) ; 2.97 (m, 1H) ; 5.77 (s, 1H).

The following examples illustrate the preparation of representative pharmaceutical formulations containing a compound of formula (I) :

For oral administration

EXAMPLE 11

Tablets with delayed release.

Unit formulation for various dosages :

Compound of formula (I)	0.50 to 10.00 mg
Aerosil® 200	0.37 to 0.50 mg
Precirol® ATO 5	1.85 to 2.25 mg
Methocel® E4	55.00 to 70.00 mg
Avicel PH® 101	10.00 to 20.00 mg
Lactose qs for 1 tablet of	185.00 to 200.00 mg

EXAMPLE 12

Fast release tablets.

Unit formulation for various dosages :

Compound of formula (I)	0.50 to 10.00 mg
Aerosil® 200	0.37 to 0.50 mg
Precirol® ATO 5	1.85 to 2.50 mg
Avicel® PH 102	50.00 to 70.00 mg
Explotab® or polyplasdone® XL	5.00 to 25.00 mg
Lactose qs for 1 tablet of	185.00 to 200.00 mg

EXAMPLE 13

Tablets.

Unit formulation for various dosages :

Compound of formula (I)	0.50 to 10.00 mg
Aerosil® 200	0.30 to 0.50 mg
Compritol®	1.50 to 3.00 mg
Avicel® PH 101	55.00 to 70.00 mg
Lactose qs for 1 tablet of	185.00 to 200.00 mg

Capsules.

Unit formulation for various dosages :

Compound of formula (I)	0.50 to 10.00 mg
Oleic acid qs for 1 capsule	250.00 to 260.00 mg
Coating : gelatine, preservatives, glycerol	

For vaginal administration

EXAMPLE 14

Vaginal gynaecologic capsule.

Unit formulation for a capsule :

Compound of formula (I)	0.50 to 15.00 mg
Vaseline	150.00 to 200.00 mg
Sorbitol sesquioleate	150.00 to 200.00 mg
Synthetic perhydrosqualene qs for 1 capsule of 1.85 g	
Coating : gelatine, glycerol, preservatives for a soft capsule weighing 2.55 g	

EXAMPLE 15

Vaginal suppository.

Unit formulation for a suppository :

Compound of formula (I)	0.50 to 15.00 mg
Witepsol® H35 or H37 qs for a suppository of 3.00 g	

EXAMPLE 16

Slow release vaginal suppository.

Unit formulation for a suppository of 3.00 g :

Compound of formula (I)	0.50 to 30.00 mg
Witepsol® H19 or H35	1.00 to 1.30 g
Suppocire® BM or NAI50	1.00 to 1.50 g
Precirol®	0.00 to 0.20 g

For cutaneous or gynaecologic use

EXAMPLE 17

Bioadhesive gel for cutaneous or gynaecologic use.

Formula for 100 g :

Compound of formula (I)	0.10 to 1.00 g
Polyethylene glycol	0.00 to 6.00 g
Transcutol®	0.00 to 6.00 g
Carboxypolyvinyl polymer	0.50 to 1.00 g
Preservatives	0.30 mg
Triethanolamine qs pH 6.5	
Purified water qs for 100 g	

EXAMPLE 18

Gel for cutaneous use.

Formula for 100 g :

Compound of formula (I)	0.10 to 2.00 g
Polyethylene glycol or Transcutol®	1.00 to 4.00 g
Ethyl alcohol	20.00 to 40.00 g
Carboxypolyvinyl polymer	0.50 to 2.00 g
Triethanolamine qs pH 6.5	
Purified water qs for 100 g	

EXAMPLE 19

Patches.

Content of the reservoir or matrix.

Preparation for 100 g

Compound of formula (I)	0.25 to 20.00 mg
Enhancer*	0.20 to 0.50 g
Suspending agent (HPMC** or Aerosil®)	0.10 to 1.00 g
Ethyl alcohol or silicone oil qs for 100 g	

* enhancer : isopropyl palmitate, propyleneglycol, menthol, azone, N,N-dimethylacetamide, mono- or disubstituted pyrrolidone derivatives ;
** HPMC : hydroxypropylmethylcellulose

For percutaneous administration

EXAMPLE 20

Implants.

Formulation for 100 g of material to be extruded :

Compound of formula (I) Polymers (EVA, polyorthocarbonates, silicone-based polymers) qs for 100 g	1.00 to 5.00 g
The temperature of the mixture shall not excede 150°C in order not to impair the active ingredient.	

Implants with reservoir.

The implant is a sealed silicone tubing of 2.5 to 3.5 cm long, 0.4 to 0.8 mm thick and 1.40 to 2mm in diameter. The preparation is formulated as a suspension as follows : For 100 g of suspension.

Compound of formula (I) Suspending agent qs for 100 g	30.00 to 50.00 g
50 mg of the suspension for one implant.	

EXAMPLE 21

Injectable depot.

Unit formulation for a flask of 5 ml.

Compound of formula (I)	10.00 to 50.000 mg
Polyethylene glycol 4000	100.00 to 200.000 mg
Preservatives	0.006 mg
Sodium chloride and citrate	0.150 mg
Distilled water for injection qs for 5.00 ml	

EXAMPLE 22

Injectable suspension.

Unit formulation for a 2 ml ampoule :

Compound of formula (I)	5.00 to 10.00 mg

Suspension solution :

Polysorbate® 80	0.015 g
Sodium carboxymethylcellulose	0.010 g
Sodium chloride	0.010 g
Purified water for injection qs for 2.00 ml	

EXAMPLE 23

Intra-uterine device with reservoir.

Device with a silicone reservoir 2.5 to 3.5 cm long and 0.4 to 0.8 mm thick. The preparation is formulated as a suspension as follows :
For 100 g of suspension.

Compound of formula (I)	0.60 to 1.00 g
suspended to :	
Suspending agent (Aerosil® or HPMC)	0.50 g
Synthetic perhydrogenalene qs for 100 g	

EXAMPLE 24

Bioadhesive gynaecological foam.

Formula for a dispenser of 50 g and a spray valve (2 ml)

Compound of formula (I)	0.10 to 0.25 g
Carboxypolyvinyl polymer	0.50 to 1.00 g
Isobutane	5.00 to 10.00 g
Excipient base F25/1 qs for 50.00 g	
Shake the suspension before use. Dispensed dosage from 2.00 to 10.00 mg	

For nasal administration

EXAMPLE 25

Nasal suspension.

Formulation for 100 g of suspension :

Compound of formula (I)	5.00 to 50.00 mg
Aerosil® PH 101	10.00 to 20.00 mg
Sodium carboxymethylcellulose	5.00 to 50.00 mg
Phenylethyl alcohol	2.00 to 10.00 mg
Polysorbate® 80	10.00 to 20.00 mg
Purified water qs for 100 g	
Shake the suspension before use Dispensed dosage from 0.5 to 2.5 mg	

For ophtalmic administration

EXAMPLE 26

Ophtalmic solution (collyrium).

Formulation for 100 g of solution. Container of 5 ml with glass droppers :

Compound of formula (I)	0.50 to 1.00 g
Glycerol	5.00 g
Polyvidone or sodium chloride	0.50 to 0.90 g
Sorbitol	4.00 g
Preservatives (benzalkonium chloride or Cetrimide®)	0.01 g
EDTA	0.01 g
Distilled water qs for 100 g	
The solution is a sterile aqueous solution ; it may contain stabilisers and antimicrobial agents. The recommended dose is one drop four times daily.	

EXAMPLE 27

Ophtalmic gel.

Formulation for 100 g of gel. Container : collapsible tube

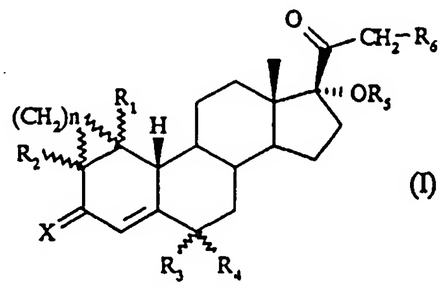
Compound of formula (I)	0.50 to 2.00 g
Cetrimide®	0.01 g
Sorbitol	4.00 g
EDTA	0.01 g
Carboxypolyvinyl polymer (Carbopol® 971)	0.14 to 0.20 g
Sodium hydroxyde 10 % qs pH 6.5	
Purified water qs for 100 g.	
The sterile aqueous gel is packed in collapsible tubes. The recommended dose is one drop one or two times daily.	

Typical examples of the compounds of formula (I) provided by this invention include :

.17α-acetoxy-6,6-dimethyl-3,20-dioxo-19-nor-pregna-4-ene
.17α-acetoxy-6β-ethyl-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene
.17α-acetoxy-6β-propyl-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene
.17α-acetoxy-1α,2α-methylene-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene
.17α-acetoxy-1β,2β-methylene-6α-methyl-3,20-dioxo-19-nor-pregna-4-ene
.17α-acetoxy-1β,2β-methylene-3E-hydroxyimino-6α-methyl-20-oxo-19-nor-pregna-4-ene
.17α-acetoxy-1β,2β-methylene-3Z-hydroxyimino-6α-methyl-20-oxo-19-nor-pregna-4-ene
.17α-acetoxy-2α,6α-dimethyl-3,20-dioxo-19-nor-pregna-4-ene
.17α-acetoxy-1α,6α-dimethyl-3,20-dioxo-19-nor-pregna-4-ene
.17α-acetoxy-1β,6α-dimethyl-3,20-dioxo-19-nor-pregna-4-ene

Claims

1. A compound of the formula (I) :



(I)

wherein :

R_1, R_2, R_3, R_4 and R_6 each independently represent hydrogen or a $(C_1$-$C_6)$alkyl,
R_5 is hydrogen, a $(C_1$-$C_6)$alkyl or a group $-COR_7$ where R_7 is a $(C_1$-$C_6)$alkyl,
n is zero or one, and
X is oxygen or an hydroxyimino group,
provided that when n = 0, at least two of R_1, R_2, R_3 and R_4 are different from hydrogen and that when n = 1, R_3 and R_4 are not simultaneously hydrogen.

2. A compound according to claim 1, wherein R_1, R_2 and R_6 are hydrogen, R_3 and R_4 are a $(C_1$-$C_6)$alkyl, R_5 is a group $-COR_7$, n is zero and X and R_7 are as defined for (I) in claim 1.

3. A compound according to claim 1, wherein R_1, R_2, R_4 and R_6 are hydrogen, R_3 is a $(C_1$-$C_6)$alkyl, R_5 is a group $-COR_7$, n is one and R_7 and X are as defined for (I) in claim 1.

4. A compound according to claim 1, wherein R_4 and R_6 are hydrogen, R_3 is a $(C_1$-$C_6)$alkyl, R_5 is a group $-COR_7$, n is zero and X, R_1, R_2 and R_7 are as defined for (I) in claim 1;

5. A pharmaceutical composition containing (i) an effective amount of a compound of formula (I) according to any one of claims 1-4 and (ii) suitable excipients.

6. A pharmaceutical composition according to claim 5, containing from 0.01 wt % to 99.99 wt% of the compound of formula (I).

7. A pharmaceutical composition according to claim 5 or 6, which is a contraceptive composition.

8. A contraceptive composition according to claim 7, which further contains an effective amount of a sex steroid.

9. Use of a compound of formula (I) according to any one of claims 1-4 for the preparation of a medicament intended for treating or preventing gynaecological disorders associated to an oestrogen/progesterone imbalance.

10. Use of a compound of formula (I) according to any one of claims 1-4 for the preparation of a medicament intended for inhibiting gonadotropic/gonadal secretions.

11. Use of a compound of formula (I) according to any one of claims 1-4, alone or in combination with a sex steroid, for the preparation of a contraceptive agent.

12. Use of a compound of formula (I) according to any one of claims 1-4, alone or in combination with an oestrogen, for the preparation of a medicament intended for postmenopausal hormone replacement therapy.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 40 0146

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	FR-A-2 111 097 (CIBA-GEIGY A.G.) 2 June 1972 * the whole document * ---	1-14	C07J7/00 A61K31/57 C07J53/00 C07J41/00 //C07J71/00, C07J21/00
Y	DE-A-20 48 231 (CIBA-GEIGY A.G.) 29 April 1971 * the whole document * ---	1-14	
Y	US-A-3 759 962 (ANNER G ET AL) 18 September 1973 * the whole document * ---	1-14	
Y	EXPERIENTIA, vol. 23, no. 10, 1967, BASEL CH, pages 794-796, XP002005533 L. A. MITSCHER ET AL: "1,2-Methylen-19-nor-17.alpha.-acetoxy-progesteron" * page 796, column 1, line 6 - line 10 * ---	1-14	
Y	DE-B-10 87 127 (SCHERING A.G.) 18 August 1960 * column 1, paragraph 2; example 3 * ---	1-14	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07J A61K
Y	DE-A-15 93 524 (SCHERING A.G.) 13 August 1970 * page 1, paragraph 1; examples 1,2B * ---	1-14	
Y	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 78, no. 11, 8 June 1956, DC US, pages 2479-2481, XP002005534 C. DJERASSI ET AL: "1-Methyl-19-norprogesterone and 1-Methyl-19-nor-17.alpha.-hydroxyprogesterone" * the whole document * --- -/--	1-14	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13 June 1996	Watchorn, P

CATEGORY OF CITED DOCUMENTS

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	FR-A-1 525 916 (SCHERING A.G.) 30 October 1968 * whole document, particularly page 2, table * ---	1-14	
Y	FR-A-1 405 214 (SOCIÉTÉ DES USINES CHIMIQUES RHÔNE-POULENC) 19 November 1965 * page 4, column 1, paragraph 3; example 38 * ---	1-14	
Y	US-A-3 835 160 (TANABE M) 10 September 1974 * column 11, line 3 - line 11; example 29 * ---	1-14	
Y	US-A-3 891 677 (TANABE MASATO) 24 June 1975 * column 7, line 1 - line 9; example 3 * ---	1-14	
Y	EP-A-0 153 270 (SCHERING AG) 28 August 1985 * the whole document * -----	1-14	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

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